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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,683	10/04/2006	Mark T. Gladwin	4239-67618-07	3225
36218 7590 04/14/2009 KLARQUIST SPARKMAN, LLP 121 S.W. SALMON STREET SUITE #1600 PORTLAND, OR 97204-2988			EXAMINER PAGONAKIS, ANNA	
			ART UNIT 1614	PAPER NUMBER
			MAIL DATE 04/14/2009	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/563,683	<b>Applicant(s)</b> GLADWIN ET AL.	
	<b>Examiner</b> ANNA PAGONAKIS	<b>Art Unit</b> 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 16 March 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) 5-12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4 and 13-16 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

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### **DETAILED ACTION**

Claims 1-4 and 13-16 are currently under examination and the subject of this Office Action.

Applicant's amendments filed 3/16/2009 has been received and entered into the present application.

Claims 1-16 are currently pending. Accordingly, claims 5-12 remain withdrawn, claim 16 is newly added and claim 15 is amended.

Applicant's arguments, filed 3/16/2009 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, has possession of the claimed invention.

Present claim 16 is directed to a method wherein the non-acidified sodium nitrite is administered to the subject in an amount and for a sufficient period of time to reach a circulating concentration in blood of the subject in less than about 25 microM, thereby treating or ameliorating the condition

In particular, the specification and claims as originally fail to provide adequate written description for the newly added claim 16. Applicant has not directed the Examiner as to where in the disclosure the

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newly added claim is found. Upon review of the instant disclosure, there seems to be no disclosure of claim 16. While it is recognized that adequate written description of a limitation is not required to be stated *in haec verba* in the specification or claims as originally filed, adequate written support for all claim limitations must arise from either an explicit or an implicit suggestion by the disclosure to show that such a concept as now claimed was actually in possession of the Applicant at the time of the invention.

MPEP §2163 states, “The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, “does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.” *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test of sufficiency of support in a parent application is whether the disclosure of the application relied upon “reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.” *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983))...Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).”

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

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***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (Abstract; J. Cereb. Blood Flow Metab. 1994, 14(2), 217-26) in view of Modin et al (Acta Physiol Scand 2001, 17, 9-16, provided by Applicant).

In the abstract, Zhang et al. teach the use of nitric oxide donors to increase blood flow and reduce brain damage in focal ischemia (title). Zhang et al. teach the nitric oxide donors sodium nitroprusside (3 mg/kg/h) and 3-morpholino-sydnonimide (1.5-6 mg/kg/h) administered into the carotid artery of rats for 60 min. Zhang et al. teach and suggest that nitric oxide donors may represent a new therapeutic strategy for the management of acute stroke.

Modin et al. teach that nitric oxide is derived from nitrite (title). Modin et al. teach that the relaxatory effect of nitrite was increased at pH 6.6 over neutral pH (abstract). Thus Modin et al. teach

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that non-acidified nitrite also has relaxatory effects similar to “acidified” nitrite (see Figures 1, 2, Figure 4 and respective discussion in text). Modin et al administered various amounts of sodium nitrite but noted a threshold response of 10 microM and near relaxation to basal tone at 1000 microM for the non-acidified sodium nitrite (page 11, Results). Modin et al. teach additional additional agents (ascorbic acid) to enhance the effect of the sodium nitrite (abstract). Modin et al in clued that inorganic nitrite evokes vasodilation most likely through nitric oxide release and that this effect is increased if the pH of the environment is reduced to levels normally found in tissues during ischemia/hypoxia (page 15, last paragraph).

The difference between the instant application and Zhang et al. is that Zhang et al. do not expressly teach non-acidified sodium nitrite in the amount of 0.6 to 240 microM. These deficiency in Zhang et al is cured by the teachings of Modin et al.

It would have been obvious to one of ordinary skill in the art at the time of the claimed invention was made to use non-acidified sodium nitrite within the range instantly claimed, as suggested by Modin et al., in the method of Zhang et al and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Zhang et al. suggest using other nitric oxide donors and Modin et al suggest how much sodium nitrite would be beneficial in tissues during ischemia. Modin et al teach carotid injection over 60 minutes of the sodium nitrite and other forms of administration such as parental, oral, buccal, rectal, ex vivo, or intraocular, peritoneal, intravenous, intraarterial, subcutaneous, inhaled, intramuscular, or cardiopulmonary bypass circuit modes of administration are not only obvious to one of ordinary skill in the art of medicine but also merely result in the same thing; increasing the blood plasma levels of sodium nitrite, in the absence of evidence to the contrary. It is the Examiner's position that rats render obvious other mammals such as humans to one of ordinary skill in the art of medicine.

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The concept of treating cerebral ischemia with nitric oxide donors to induce vasodilation and/or increase blood flow is established in the art. Non-acidified sodium nitrite is known to a nitric oxide donor in the art. Applicant has merely followed the suggestions of Zhang et al and Modin et al to use sodium nitrite in the treatment of cerebral ischemia. The predictable expected result is induced vasodilation and increased blood flow in the subject.

From recent case law: "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." (KSR INTERNATIONAL CO. v. TELEFLEX INC. ET AL. 550 U.S. \_\_\_\_ (2007) page 24).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings (In re Opprecht 12 USPQ 2d 1235, 1236 (Fed. Cir. 1989); In re Bode 193 USPQ 12 (CCPA) 1976).

In light of the foregoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time of the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

With regard to claim 16, it is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

*Applicant's Remarks*

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Applicants respectfully submit that Zhang et al, Modin and Nachtsheim fail to satisfy the requirements for a finding of obviousness of claims 1-4 and 13-15. Applicant alleges that nitric oxide donors behave differently and that the Office must provide evidence that one of ordinary skill would have a reasonable expectation that sodium nitrite could be used as an equivalent substitute for SNP or SIN. Further, Applicant's alleges that the experiments conducted by Modin were in aortic ring bioassays without circulating blood and as such do not reflect what would happen in the human circulation. Applicant cites Isbell et al and Crawford et al in support that aortic ring bioassays are not predictive. Applicant alleges that Modin teaches that acidified inorganic nitrite is preferred and therefore non-acidified is not. Applicant's cite Laur, Rassaf and Modin in support that aortic ring bioassays are poor systems in which to study the in vivo vasodilatory effects of sodium nitrite.

*Remarks to Applicant's Arguments*

Applicant's amendments and remarks have been carefully considered in their entirety, but fail to be persuasive in establishing error in the propriety of the present rejection.

Firstly, the Examiner clearly states that both SNP and non-acidified sodium nitrite are well known as nitric oxide donors. Applicant's alleges that the two above mentioned nitric oxide donors have different mechanisms of action, but advances no specific reason or evidence that even if different mechanisms of action do exist why varying mechanisms of action render the rejection non-obviousness. Applicant advances Counsel's own speculation in support of this position. This assertion by Counsel is an unsupported allegation and fails to take place of evidence in the record. Statements of this nature are clearly unpersuasive in accordance with guidance provided at MPEP 2145, which states, "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602 145 USPQ 716, 178 (CCPA 1965); *In re Geisler* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)." Arguendo the above, even if different mechanisms of action do exist, Applicant's have not set forth whether this difference does not produce the same result, i.e. nitric oxide donation.



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Secondly, it is noted that neither Isbell nor Crawford conclude that aortic ring bioassays are not predictive and therefore the references are unpersuasive. Further, though Applicant states that the in vitro environment of the Modin experiments is also not predictive, Modin clearly provides motivation by stating that in vivo studies can be conducted in the future to confirm non-enzymatically derived NO contributes to the 'metabolic-acidic' local blood flow regulation (page 15, column 1). Additionally, it is clear that Modin attempted to provide a cultured environment mimicing of an in vivo setting for instance by maintaining an organ bath for the aorta.

Applicants conclusion that acidified inorganic nitrite is preferred by Modin and therefore that non-acidified is not effective is again Counsel's own speculation. No where does Modin set forth such reasoning. With regard to Applicant's position that no credible support exists that one of skill would use non-acidified sodium nitrite of Modin in the method of Zhang, the obviousness rejection on pages 3-4 of the Office Action mailed 10/15/2008 is noted.

It is noted that neither Lauer nor Rassaf conclude that aortic ring bioassays are poorly predictive of the in vivo environment. It is noted that neither study administered the instantly claimed non-acidified nitric oxide, as neither does McMahon.

Finally, Applicant is again reminded that rejections made under 35 U.S.C. 103(a) are based upon the combination of references. As a result, focusing solely on the discrete teachings of each of the cited references is tantamount to examining each of them inside of a vacuum and fails to be persuasive in establishing non-obviousness, not each individual reference alone. In other words, it must be remembered that the references are relied upon in combination and are not meant to be considered separately. To properly conclude obviousness of an invention does not require the claimed invention to be expressly suggested in its entirety by any one single reference under 35 U.S.C. 103(a). Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.

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***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 13-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6-13 and 20-23 of copending Application No. 10/563,682. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the instant invention embraces or is embraced by the subject matter of the copending application. One of ordinary skill in the art would recognize the methods in the copending application of treating cerebral ischemia by decreasing blood pressure or increasing vasodilation with a non-acidified sodium nitrite to a subject as embracing the subject matter of instant claims 1-4, 13-15. The same concentrations of sodium nitrite are claimed as well as the subjects and routes of administration.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

*Applicant's Remarks*

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Applicant states that, since none of the copending applications have been allowed, the instant rejections should be withdrawn without the need of a Terminal Disclaimer should they be the only rejections remaining in the present case.

*Response to Applicant's Arguments*

In the absence of additional remarks to the contrary or any Terminal Disclaimers, and further in light of the fact that these rejections are not the only rejections that remain, the rejections of the present claims over each of the cited copending applications remain proper at this time.

**Conclusion**

No claim is found to be allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Ardin Marschel/  
Supervisory Patent Examiner, Art Unit 1614